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| EXAMINER |
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| O HARA, EILEEN B |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1646 | |

DATE MAILED: 02/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Application No. | Applicant(s) |
|---|---|
| 09/882,735 | FISHER ET AL. |
| **Examiner** | **Art Unit** |
| Eileen B. O'Hara | 1646 |

## *Office Action Summary*

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *02 December 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *3,13-21,26,27,29 and 30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-12,22-25,28 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-31* are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4)☐ Interview Summary (PTO-413) Paper No(s). _____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

## DETAILED ACTION

1. Claims 1-31 are pending in the instant application. Claims 1 and 3 have been amended as requested by Applicant in Paper Number 11, filed Dec. 2, 2002.

2. Applicant's election with traverse of Group A, claims drawn to the sTNFR polypeptide of SEQ ID NO: 2, and species of truncated sTNFR polypeptide comprising amino acid residues 1-105 of SEQ ID NO: 2 and further comprising an amino-terminal methionine (SEQ ID NO: 8) in Paper No. 11 is acknowledged. The traversal is on the ground(s) that there will be no undue hardship on the Office in performing a search with respect to the sTNFR-I polypeptides of SEQ ID NOS: 2, 4, 6, 8, 10, 12 and 14, since they share 100% sequence identity with residues 19-104 of the sTNFR-I polypeptide of SEQ ID NO: 2. This is found persuasive in view of this argument and the sequence alignment presented in Exhibit A, and all of the truncated sTNFR-I polypeptides of SEQ ID NOS: 2, 4, 6, 8, 10, 12 and 14 will be examined. Upon further consideration, claims encompassing polyvalent forms of these polypeptides will also be examined.

The requirement is still deemed proper and is therefore made FINAL.

Claims 3, 13-21, 26, 27, 29 and 30 are withdrawn as being drawn to a non-elected invention.

Claims 1, 2, 4-12, 22-25, 28 and 31 are currently under examination.

***Priority***

3. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) and 120 as follows: An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78) and the current status of the prior application(s).

***Claim Objections***

4.1 Claims 2 and 4-12, 22, 24, 25, 28 and 31 are objected to because of the following informalities:

a) Claims 2 and 4-12 are missing the word "factor" after the words "tumor necrosis".

b) Claims 4-12, 22, 24, 25, 28 and 31 depend from a claim encompassing a non-elected invention.

4.2 Claims 6-8, 11-12, 23, 28 and 31 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n).

4.3 Claim 10 is objected to because of the following informalities:

37 C.F.R. §1.821(d) states:

> Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

Sequences are disclosed in claim 10 (sTNFR-I 2.6D C105db and sTNFR-I 2.6D C106db) without the required reference to the sequence identifiers (SEQ ID NOS:). For rules interpretation Applicant may call (703) 308-1123. See M.P.E.P. 2422.04.

Applicants are required to amend the specification and claims to comply with 37 C.F.R. §1.821(d).

4.4 Claims 11 and 12 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Intended use is not further limiting of the compound.

Appropriate correction is required.

***Claim Rejections - 35 USC § 101***

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5. Claims 2, 4 and 5 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claim 2 encompasses a tumor necrosis factor binding protein comprising the amino acid sequence of SEQ ID NOS: 4, 6, 8, 12, 10 or 14, or a variant thereof. The amino acid sequences of SEQ ID NOS: 4, 6, 8, 12, 10 and 14 are all smaller portions of the protein of SEQ ID NO: 2 (which comprises amino acids 20-161 of the mature full-length or soluble TNFR-1) with the addition of a methionine at the amino terminal end (which is normally an arginine in the full length TNFR sequence), and in the case of SEQ ID

NO: 4 additionally a substitution of the asparagine at position 105 with a cysteine. The specification describes "variants" of truncated sTNFRs on pages 19-22 as proteins having amino acids deleted, inserted into or substituted for amino acids in the proteins. The naturally occurring non-isolated full-length TNFR-1 or naturally occurring soluble form of TNFR comprises polypeptides that are variants of the proteins of SEQ ID NOS: 4, 6, 8, 12, 10 and 14. The rejection would be withdrawn by limiting claim 2 to "isolated" proteins.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6.1 Claims 1, 2, 4-12, 22-25, 28 and 31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification describes truncation variants of the polypeptide of SEQ ID NO: 2, which is the extracellular domain of human Tumor Necrosis Factor Receptor-1, which is composed of four cysteine rich domains. Amino acids 1-161 of SEQ ID NO: 2 correspond to amino acids 20-180 of the human TNFR-1 (p55) (The Cytokine Facts Book, page 245). The instant application teaches that the prior art had taught that a truncated TNFR that had the fourth domain deleted would still bind TNF, but that deletion variants having the first, second or third domains deleted could not bind TNF. The proteins of the instant invention are drawn to truncation variants of SEQ ID NO: 2 that still bind

TNF and which do not contain the fourth domain (amino acids 127-161 of SEQ ID NO: 2), a portion of the third domain (amino acids (111-126 of SEQ ID NO: 2, approximately half of the third domain) and optionally, do not contain a portion of the first domain (amino acids 1-19 of SEQ ID NO: 2, approximately half of the domain). SEQ ID NOS: 4, 6, 8, 10, 12 and 14 are some of these truncated proteins (Exhibit A, filed Dec. 3, 2002). However, the claims as written include polypeptides comprising variants and homologues, and encompass polypeptides that vary substantially in length and also in amino acid composition. The instant disclosure of a single polypeptide, that of SEQ ID NO: 2 and the carboxy and amino terminal truncations, with the instantly disclosed specific activity of binding TNF, does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), which states:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention". Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1980) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d 1565, 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by

structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id at 1170, 25 USPQ2d at 1606."

A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. The instant specification discloses, however, a single isolated polypeptide sequence SEQ ID NO: 2 and the specific truncation proteins derived from this polypeptide. The specification includes in the "variants" of the invention allelic variants, and insertion, deletion and substitution variants. There are no allelic variants of SEQ ID NO: 2 disclosed in the specification, and the only insertion, deletion or substitution variants are those of SEQ ID NOS: 4, 6, 8, 10, 12 and 14, which either have an additional methionine at the amino terminus end or a single amino acid substitution at the carboxy terminus, both of which are not necessary for TNF binding. There are no examples of any insertions, deletions or substitutions in the core binding region (amino acids 19-104 of SEQ ID NO: 2) common to all the polypeptides. Receptor function, cannot be reliably predicted from protein sequence information alone. For example, vertebrate growth hormone of 198 amino acids becomes an antagonist (inhibitor of growth) when a single amino acid is changed (Kopchick et al, U.S. Patent No. 5,350,836). Even 99% homology does allow predictability in this instance. Given the unpredictability of changing amino acid sequence on function, and the fact that the specification fails to provide objective evidence that the additional sequences are indeed species of the

claimed genus it cannot be established that a representative number of species have been disclosed to support the genus claim. No activity is set forth for the additional sequences. Further, even if the proposed consensus sequence were definitive of a genus with a specified function, the instantly claimed genus is not so limited and the prior art does not provide compensatory structural or correlative teachings to enable one of skill to identify the polypeptides encompassed.

6.2 Claims 1, 2, 4-12, 22-25, 28 and 31 are also rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and using a polypeptide of SEQ ID NO: 2 and polypeptides comprising the truncation variants of the polypeptide of SEQ ID NO: 2, does not reasonably provide enablement for making and using polypeptide variants of these polypeptides. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Because these claims encompass the variants stated above, and only one polypeptide with the core TNF binding sequence has been disclosed in the instant specification, a practitioner can not make a protein comprising an amino acid sequence having a core TNF binding sequence other than the one disclosed in the instant specification and expect it to have the same function of binding TNF. However, the instant specification does not identify those amino acid residues in the amino acid sequences of SEQ ID NOS: 2, 4, 6, 8, 10, 12 and 14 which are essential for its biological activity and structural integrity and those residues which are either expendable or substitutable. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid

substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions. However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. In the absence of this information a practitioner would have to resort to a substantial amount of undue experimentation in the form of insertional, deletional and substitutional mutation analysis before they could even begin to rationally design a functional protein having other than a natural amino acid sequence. The disclosure of a single polypeptide with a natural amino acid sequence is clearly insufficient support under the first paragraph of 35 U.S.C. § 112 for claims which encompass the other variants. Even acknowledging high

skill in the molecular biology art, prediction of which variants would bind TNF is not possible based on the prior art or on the information provided in the specification, and the specification has not taught how to use a variant that does not bind TNF.

The current claim limitations are analogous to those of claim 7 of U.S. Patent Number 4,703,008 which were held to be invalid under 35 U.S.C. § 112, first paragraph, for want of enablement in *Amgen Inc. v. Chugai Pharmaceuticals Co. Ltd.*, 18 U.S.P.Q. 2d, 1016 (CAFC, 3/5/91, see page 1026, section D). In that instance, a claim to a nucleic acid encoding a polypeptide having an amino acid sequence sufficiently duplicative of the amino acid sequence of erythropoietin (EPO) so as to have a specified biological activity was held to be invalid under 35 U.S.C. § 112, first paragraph, for want of enablement. The disclosure upon which that claim was based described a recombinant DNA encoding EPO and a few analogs thereof. That disclosure differs from the instant specification because, whereas the instant specification describes truncation variants of naturally occurring human TNFR1 protein, it does not describe even a single variant thereof that has non-naturally occurring sequence outside of the core TNF binding region. The court held that what is necessary to support claims of this breadth is a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of the claims. For proteins, that means disclosing how to make and use enough sequences to justify the grant of the claims sought. As indicated, the instant specification is even more limited than the '008 patent because it describes only a single protein and no analogs or mutants thereof in the core TNF binding region and, therefore, provides even less support than the '008 specification for claims of comparable scope and which were held to be invalid in that patent.

There are many factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue. These factors

include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988).

For the reasons discussed above, due to the large quantity of experimentation necessary to generate the large number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples and written description directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any specific functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1, 2, 4-12, 22-25, 28 and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1, 2, 4-12, 22-25, 28 and 31 encompass "derivatives" of sTNFR polypeptides, and although the specification at page 33, line 21

discusses different derivatives, the term is still indefinite because the metes and bounds of what a derivative is not defined.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claim 2 is rejected under 35 U.S.C. 102(b) as being anticipated by Thompson et al., WO 92/16221, Oct. 1, 1992. Claim 2 encompasses a tumor necrosis factor binding protein comprising the amino acid sequence of SEQ ID NOS: 4, 6, 8, 12, 10 or 14, or a variant thereof.

Thompson et al. disclose a 30kDa TNF binding protein that is 100% identical to SEQ ID NO: 2 of the instant application. The amino acid sequences of SEQ ID NOS: 4, 6, 8, 12, 10 and 14 are all smaller portions of the protein of SEQ ID NO: 2 with the addition of a methionine at the amino terminal end, and in the case of SEQ ID NO: 4 additionally a substitution of asparagine at position 105 with a cysteine. The specification describes variants of truncated sTNFRs on pages 19-22 as proteins having amino acids deleted, inserted into or substituted for amino acids in the proteins. The protein of Thompson et al. comprises a variant sequence of the proteins of SEQ ID NOS: 4, 6, 8, 12, 10 and 14, and therefore anticipates the claim.

The art considered pertinent to the present application is Chen et al., Journal of Biological Chemistry, Vol. 270, No. 6, pages 2874-2878, February 1995, which discloses that the fourth

cysteine rich domain of the extracellular region of p55 TNF receptor is not necessary for TNF binding, but the third domain is.

***Conclusion***

9. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (703) 308-3312. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (703) 308-6564.

Official papers Before Final filed by RightFax should be directed to (703) 872-9306.

Official papers After Final filed by RightFax should be directed to (703) 872-9307.

Official papers filed by fax should be directed to (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Eileen B. O'Hara, Ph.D.

Patent Examiner